

**REMARKS**

Claims 23-26, 30-31, 42-46, 48 and 50-52 are pending and under examination in the above-identified application. Applicant has review the rejections set forth in the Office Action mailed January 30, 2004, and respectfully traverse all grounds for the reasons that follow.

Applicant would like to thank Examiner Forman for extending a personal interview with Applicant's representatives on March 24, 2004. As recorded in the Interview Summary, the rejection under 35 U.S.C. § 103(a) was discussed. The remarks below are believed by Applicant to substantially conform to the subject matter discussed in the interview.

**Rejections Under 35 U.S.C. § 103**

Claims 23-26, 30, 31, 42-46, 48, 50 and 52 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Nikiforov et al., U.S. Patent No. 5,952,174, in view of Weisburg et al., U.S. Patent No. 6,110,678. Dependent claims 29, 49 and 51 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Nikiforov et al., *supra*, in view of Weisburg et al., *supra*, as applied to base claim 42, and further in view of Walt et al., U.S. Patent No. 6,327,410.

Nikiforov et al. is alleged to describe a method of determining the identification of a nucleotide at a detection position using capture probes that hybridize to a ligation product. The Office concedes that Nikiforov et al. fails to describe a substrate with a surface comprising discrete sites and a population of microspheres comprising first and second subpopulations of capture probes. Weisberg et al. is alleged to describe such a substrate. The Office concludes that it would have been obvious to modify the capture probe hybridization method described by Nikiforov et al. by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg et al. to optimize environmental conditions for each method step as suggested by Weisberg et al. for the obvious benefit of maximizing experimental results. *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) is cited as authority for the asserted motivation of optimizing

environmental conditions, purporting to state that where general conditions of a claim are disclosed in the art, it is not inventive to discover the optimum by routine experimentation.

Applicant respectfully submits that *In re Aller* fails to support a motivation to combine the cited references to obtain the claimed invention. In this regard, *In re Aller* addressed the patentability of a claimed process where the only distinction over the cited art was a difference in the concentration or temperature of the claimed process. The court stated that unless there is evidence indicating that such concentration or temperature is critical, it is not inventive to discover the optimum or workable ranges by routine experimentation. *Id.* Therefore, *In re Aller* was specifically directed to the patentability of a claim which relied on optimum concentrations or temperature or optimum ranges of concentration or temperature.

Although encompassing species of improvements in concentrations and temperature optimums or workable ranges, the invention neither specifically claims an improvement constituting an optimum in concentration or temperature nor a specific workable range of concentration or temperature. Rather, the claimed invention is directed to an unobvious series of hybridization, extension, ligation and detection steps, without recitation of concentration or temperature optimums or workable concentrations or temperature ranges. Therefore, *In re Aller* is inapplicable for supporting the Office's rejection. Further, if the Office maintains the rejection based on *In re Aller* as authority, Applicant respectfully requests that the Office articulate and support why the claimed invention is viewed as claiming a concentration or temperature optimum.

Further, Applicant claims a method of determining the identification of a nucleotide at a detection position in a target sequence. The method includes providing a hybridization complex where a first ligation probe is hybridized to a first target domain that is directly 5' to a detection position and a second ligation probe is hybridized to a second target domain that is 3' adjacent to the detection position. The hybridization complex is extended such that a dNTP is perfectly complementary to the base at the detection position, ligated to form a ligation product and detected using a substrate with a

surface containing discrete sites and a population of microspheres containing first and second subpopulations containing capture probes that hybridize to the ligation product. The claimed method steps are neither described or suggested in the cited art to Nikiforov et al. and Weisburg et al.

The Office asserts that Weisburg et al. provides the motivation to modify the method of Nikiforov et al. by providing microspheres having capture probes to “optimize environmental conditions” for each method step for the “obvious benefits of maximizing experimental results.” Office Action at pages 4 and 14. The Office asserts that the method of Weisburg et al. allows target-probe and target-capture probe hybridization to occur under different environmental conditions and permits optimization of both hybridization environment and capture environment. Column 4, line 57 through column 5, line 19, and particularly column 5, lines 1-19 are cited as support. However, the cited language in Weisburg et al. fails to describe any method of optimization. Specifically, Weisburg et al. state:

The present invention features methods for capturing a target polynucleotide onto a solid support using a capture probe and two different hybridization conditions. Different hybridization conditions are used to control the order of hybridization in a sample containing a target polynucleotide, mixed with a capture probe and an immobilized probe. By a “hybridization condition” is meant the cumulative environment used for a reaction in which one single-stranded nucleic acid hydrogen bonds to a second single-stranded nucleic acid to produce a hybridization complex (which is sometimes referred to herein as a “complex”). The cumulative environment includes, for example, the concentrations and components (e.g., salts, chelating agents and noncompetitive inhibitor nucleic acids) of an aqueous or organic solution containing the single-stranded nucleic acids, and the temperature of the reaction mixture. Other factors that may contribute to the cumulative environment include, for example, the amount of time in which hydrogen bonding is allowed to occur, the physical geometry of the chamber holding the reactants, and the use of mixing or agitation during hybridization. All of these environmental conditions are well known in the art (e.g., See Sambrook et al., *Molecular Cloning. A Laboratory Manual*, 2<sup>nd</sup> ed. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989)). In the present invention, the first hybridization condition facilitates hybridization of the capture probe to the target polynucleotide while essentially precluding hybridization of the capture probe and the immobilized probe, and a second hybridization

condition then facilitates hybridization of the capture probe and the immobilized probe.

Col. 4, line 57 through col. 5, line 19.

The language above in Weisburg et al. is directed to a method of ordering the hybridization of probes to a target sequence. Weisburg et al. describe the method as using “two different hybridization conditions . . . to control the order of hybridization in a sample.” The word “optimization” or a description of optimal conditions is missing from the cited text. Similarly, the phrases relied on by the Office for supporting the assertion that Weisburg et al. suggests optimizing environmental conditions, such as “maximizing experimental results,” also is not found in the cited text. Rather than describing optimization of a condition, Weisburg et al. instead describes a procedure that requires two different conditions to work, if the procedure is to work at all. Accordingly, the assertion that Weisburg et al. optimizes hybridization or that Weisburg et al. provides motivation to combine its description with that of Nikiforov et al. premised on a description of optimal procedures is unfounded.

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The first prong of this test is unsatisfied because the Office simply asserts that the method Weisburg et al. (1) optimizes environmental conditions for (2) the obvious benefit of maximizing experimental results. However, there has been no showing that such a general conclusion is supported by the cited art, particularly in light of the language cited by the Office.

Further, establishing that the prior art would have suggested the claimed invention requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an “essential evidentiary component of an obviousness holding.” *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (quoting *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); see also *C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art

where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not “evidence.” *Brown & Williamson Tobacco*, 229 F.3d at 1125 (quoting *In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)). One purpose of the evidentiary requirement for showing a suggestion, motivation or teaching of the claimed combination is to prevent impermissible hindsight reconstruction of the claimed invention based on Applicant’s own disclosure. *C.R. Bard*, 157 F.3d at 1352; *In re Dembiczak*, 175 F.3d 994, 999 (“[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight”).

In the pending Office Action, there has been no underlying factual showing that it would have been obvious to one of ordinary skill in the art to have modified the method of Nikiforov et al. with the microspheres of Weisburg et al. The required evidentiary showing, pointing to some motivation, suggestion or teaching in the prior art of the desirability of making the specific modification, in particular, addition of the microspheres, that was made by the inventors is lacking from the assertions in the Office Action. While the Office provides “obvious benefits of maximizing experimental results,” premised on a purported “optimiz[ation] of environmental conditions” as providing the motivation for providing the missing element of microspheres, the federal case law requires that the evidentiary showing be clear and particular and does not allow for broad conclusory statements about the teachings of the cited references. Absent such evidence, the Office is impermissibly relying on hindsight. Accordingly, the cited art to Nikiforov et al. and Weisburg et al. fail to teach, suggest or provide a motivation for one skilled in the art to carry out the claimed invention with a reasonable expectation of success.

The Office further asserts that Applicant's previous arguments were unpersuasive with respect to the number of probes required to be used if the methods of Nikiforov et al. and Weisburg et al. would be combined and with respect to the inoperability of such a combination because such Applicant's arguments do not address limitations of the claims.

Applicant respectfully disagrees and resubmits that Applicant's previous arguments were directed to the lack of a teaching, suggestion or motivation to combine the method of Nikiforov et al. with the microspheres of Weisburg et al. to obtain the claimed method. Because the number of probes required would differ compared to the claimed invention and because such a combination of Nikiforov et al. and Weisburg et al. would be inoperable, Applicant directly addressed the claimed invention. Absent operability or a combination that would derive Applicant's invention as claimed, any asserted combination of references fails to provide the proper factual showing of a motivation to combine to obtain the claimed invention. Therefore, reconsideration of these arguments is respectfully requested.

In light of the remarks above, Applicant contends that the claimed invention is unobvious over the cited art. Accordingly, Applicant respectfully requests withdrawal of the rejection under § 103 over Nikiforov et al. in view of Weisburg et al., or with respect to dependent claims 29, 49 and 51, over Nikiforov et al. in view of Weisburg et al. and Walt et al

In *Graham v. John Deer Co.*, the Supreme Court held that consideration of secondary indicators of nonobvious is required. 383 U.S. 1, 17-18 (1966). *Graham* listed (1) commercial success, (2) long-felt but unsolved need and (3) failure of others as indicators to be considered. *Id.* Other secondary indicators also have been considered, including (1) skepticism or disbelief before the invention (*Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697-98 (Fed. Cir. 1983) as well as (2) copying, praise, unexpected results and industry acceptance (*Allen Archery, Inc. v. Browning Mfg. Co.*, 819 F.2d 1087, 1092 (Fed Cir. 1987); *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000)). When considering commercial

success, a nexus between the commercial success and the claimed features is required. *Id.* at 1130. Applicant has supplied evidence, in the form of a declaration, for both commercial success and industry acceptance as well as for the required nexus.

As previously made of record in the declaration by John Stuelpnagel and as reaffirmed in Applicant's previous response, the declaration attests that Illumina's product uses the methods claimed in the above-identified application for identification of nucleotides at a detection position. Specifically, the declaration states:

The current system for genotyping at Illumina utilizes labeled probes that are part of a hybridization complex with a capture probe on a surface. Specifically, ligation and extension assays are currently run. **Thus, Illumina specifically utilizes the methods outlined in the claims.**

Stuelpnagel Declaration dated April 30, 2002, paragraph 5, emphasis added. Therefore, the nexus between the commercial product and the claimed invention has been established.

The declaration also attests that there has been commercial success as well as industry acceptance. At paragraph 6 of the declaration, John Stuelpnagel states "Illumina's SNP Genotyping services are commercially successful." Further, the Illumina services embodying the claimed method are stated to have been or are currently being sold to (1) GlaxoSmithKline, (2) Johns Hopkins Medical University, (3) Institute of Genetic Medicine, (4) Boston University Medical Center, (5) University of California, San Diego, (5) Oxagen and (6) other undisclosed customers. Declaration at paragraph 4. Therefore, more than seven entities have purchased the services embodying Applicant's claimed method. The above evidence, together with Applicant's subsequent submission of the publication summarizing the HapMap project (*MIT Technology Review* 6:42 (2003), submitted as Exhibit A to Applicant's response filed July 25, 2003), showing that Illumina's product and method therein constitutes greater than 50% of the project users show both that Applicant has achieved commercial success as well as industry acceptance.

Accordingly, two factors articulated by *Graham* and its progeny, and required to be considered as indicators of nonobvious, have been substantiated. The required nexus

for commercial success of the claimed invention and the product also as been substantiated. Based on the lack of any motivation to combine the cited art to obtain the claimed invention alone or in combination with Applicant's showing of secondary indicia of nonobviousness, Applicant submits that the invention as claimed is patentable over the cited art. Therefore, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

### **Obvious-Type Double Patenting Rejection**

Applicants respectfully traverse the rejection of claims 29-31, 42-43, and 46-48 as unpatentable over claims 1-7 and 27-30 of U.S. Patent No. 6,355,431, under the judicially created doctrine of obviousness-type double-patenting.

Applicants respectfully submit that claims 29-31, 42-43, and 46-48 are patentably distinct from claims 1-7 and 27-30 of U.S. Patent No. 6,355,431. Base claim 42 and its dependent claims are directed to a method of determining the identification of a nucleotide at a detection position via method steps that are unobvious over base claim 1 and its dependent claims, which are directed to a method for detecting a target nucleotide sequence rather than identifying a nucleotide. In contrast to the Office's assertions, the open-ended claim term "comprising" does not defeat the nonobviousness of the claimed method steps compared to that of the '431 patent. The general assertion that the claim language encompasses detection fails to support how the method steps of the claimed invention are obvious over the '431 patent. Accordingly, the claims are directed to different, patentably distinct methods.

Accordingly, Applicants request removal of the rejection of claims 29-31, 42-43, and 46-48 as unpatentable over claims 1-7 and 27-30 of U.S. Patent No. 6,355,431, under the judicially created doctrine of obviousness-type double-patenting.

### **CONCLUSION**

In light of the Remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.



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To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read "D.A. Gay", written over the printed name.

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